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| 10/083,340 | 02/27/2002 | Hideki Kambara | ASAM.0055 | 8243 |

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| EXAMINER |
|---|
| FREDMAN, JEFFREY NORMAN |

| ART UNIT | PAPER NUMBER |
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| 1634 | |

DATE MAILED: 03/02/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/083,340 | KAMBARA ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey Fredman | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *15-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/05/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of Group I, claims 1-14, 25 and 26 in the paper filed January 12, 2004 is acknowledged.

### *Priority*

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The case is on the USPTO electronic system and the priority documents were received but not placed in the electronic file (though it appears to be properly received and is of record). Since the foreign priority document is a Japanese Application, the examiner will assume that it is not in English and cannot be reviewed for support for purposes of intervening art.

### *Claim Rejections - 35 USC § 112*

3. Claims 1-14 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the final step (4) is vague and indefinite because there is no connection in the final phrase between the detection of luminescence and the detection of the mutations. The claim fails to indicate that the mutations are detected based upon the luminescence, and therefore it is unclear if the claim intends separate detection of the luminescence and of the mutations or detection of the luminescence which results in detection of the mutation. If they are independent, then the claims require some other mode of determining the mutation present in the target nucleotide sequences.

Claim 6 is simply unclearly written. It is simply impossible to properly analyze this claim given the indefinite nature of the subject matter. For example, something "is used for the synthesis of complementary strands", but from the claim structure, it is impossible to tell whether this is the anchor primers having the first arbitrary sequence, the second anchor primer, the remaining region or something else. This claim must be rewritten to improve it's clarity.

Claim 9 lacks antecedent basis for the term "the circular DNA" and it is entirely unclear what this term means in this claim.

Claim 13 appears to contradict the method claim 1 from which it depends since it forms pyrophosphate that is not relevant to the mutation of interest. This claim therefore is read as simply extension that creates pyrophosphate.

Claim 25 lacks antecedent basis for terms such as "said primers" in line 2.

4. The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 13 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Ahmadian (Anal. Biochem. (2000) 103-110).

Ahmadian teaches a method for examining nucleotide sequences (see abstract) comprising:

(1) adding a group of primers consisting of multiple primer species (see table 1, page 104), to a solution containing a sample subjected to examination (see page 104, column 1), and performing simultaneous synthesis of complementary strands at each of the multiple regions containing target nucleotide sequences to be examined (see page 104, column 1, where the multiplex PCR synthesizes complementary strands at multiple regions with multiple primers),

(2) designing DNA probes with specific sequences that are adjacent to polymorphisms (cf mutations) (see page 104, table 1),

(3) performing elongation reaction of complementary strands using said targets or the sequences complementary to said targets as a template and the following reaction in which pyrophosphate produced during the elongation reaction is converted to ATP and reacted with a chemiluminescent substrate to develop luminescence (see page 104, column 2, subheading "pyrosequencing") in subcells of a reaction vessel that are compartmentalized for each target (see abstract, "Here, we demonstrate that typing of SNPs can efficiently be performed by pyrosequencing using an automated system for parallel analysis of 96 samples in approximately 5 min, suitable for large scale screening and typing of SNPs", which expressly teaches the use of 96 samples and page 108, column 1 teaches a microtiter dish that represents compartmentalized subcells),

(4) detecting said luminescence, mutations present in said target nucleotide sequence (see figure 4, for example and page 104, column 2).

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-10, 12, 13, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmadian (Anal. Biochem. (2000) 103-110) in view of Barany et al (U.S. Patent 6,027,889).

Ahmadian teaches a method for examining nucleotide sequences (see abstract) comprising:

(1) adding a group of primers consisting of multiple primer species (see table 1, page 104), to a solution containing a sample subjected to examination (see page 104,

column 1), and performing simultaneous synthesis of complementary strands at each of the multiple regions containing target nucleotide sequences to be examined (see page 104, column 1, where the multiplex PCR synthesizes complementary strands at multiple regions with multiple primers),

(2) designing DNA probes with specific sequences that are adjacent to polymorphisms (cf mutations) (see page 104, table 1),

(3) performing elongation reaction of complementary strands using said targets or the sequences complementary to said targets as a template and the following reaction in which pyrophosphate produced during the elongation reaction is converted to ATP and reacted with a chemiluminescent substrate to develop luminescence (see page 104, column 2, subheading "pyrosequencing") in subcells of a reaction vessel that are compartmentalized for each target (see abstract, "Here, we demonstrate that typing of SNPs can efficiently be performed by pyrosequencing using an automated system for parallel analysis of 96 samples in approximately 5 min, suitable for large scale screening and typing of SNPs", which expressly teaches the use of 96 samples and page 108, column 1 teaches a microtiter dish that represents compartmentalized subcells),

(4) detecting said luminescence, mutations present in said target nucleotide sequence (see figure 4, for example and page 104, column 2).

Ahmadian does not teach the use of anchor primer PCR where gene specific primer amplification with 5' anchor tails is followed by amplification by the anchor primers.

Barany teaches a method of examining nucleic acid sequences (see abstract) comprising:

(1) providing a group of primers which consist of a first gene specific region and a second arbitrary anchor (zip code) sequence at the 5' terminus that is not hybridized with the targets (see figure 5 and column 16, lines 49-67),

(2) removing excess primers by creating a second PCR reaction (see figure 5 and column 17),

(3) providing anchor (zip code) primers that hybridize to the complementary strand (see figure 5 and column 17)

(4) preparing DNA stands with the first and second anchor (zip code) sequences (see figure 5 and column 17),

(5) amplifying DNA stands with the first and second anchor (zip code) sequences (see figure 5 and column 17).

With regard to claims 3-4, Barany teaches hybridization of the DNA probes to the mutation sites where elongation by ligation depends upon the base species at the putative mutation site (see figure 11).

With regard to claims 5, 7-10, 12, and 26, Barany teaches a method of easily distinguishing between the primers which detect mutant and wildtype by binding to an array with immobilized DNA at different sites (see figure 13, where each probe is captured on an addressable array). Barany also notes that the hybridization method may be performed at temperatures up to 90C (see column 36, line 25).

With regard to claim 6, this claim is sufficiently indefinite, for the reasons given above, that it appears that Barany teaches PCR amplification with the anchor sequences, which appears to meet this indefinite claim.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the coupled PCR methods of Barany for determination of nucleotide differences to the method of Ahmadian since Ahmadian notes that the limiting factor in the method is template preparation, stating ""The limiting factor is not the SNP analysis but rather the template preparation. In order to score thousands of SNPs simultaneously, novel approaches are needed". So Ahmadian states, as a desire, a wish for fast, efficient template preparation. Barany provides a solution to this problem, by performing the coupled PCR reactions which Barany notes are advantageous over the use of PCR alone as used by Ahmadian (see column 7, lines 35-38). Barany further expressly notes that "The primary PCR/secondary PCR/LDR process of the present invention is able to achieve multiplex detection of hundreds of nucleotide sequence differences in a single tube without undue customization of operating conditions for each particular sample being analyzed. (see column 8, lines 63-68)." So an ordinary practitioner, faced by Ahamadian with the express concern and problem of template preparation for SNP analysis, would have turned to Barany, who solves this problem in a way superior to PCR alone that will detect the hundreds of SNPs of Ahmadian in a single tube.

10. Claims 11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahmadian (Anal. Biochem. (2000) 103-110) in view of Barany et al (U.S. Patent

6,027,889) as applied to claims 1-10, 12, 13, 25 and 26 above and further in view of Dzieglewska et al (WO 98/28440)

Ahmadian in view of Barany teach the limitations of claims 1-10, 12, 13, 25 and 26 as discussed above. Ahmadian in view of Barany do not teach the use of loop primers in the pyrophosphate SNP detection method.

Dzieglewska teaches the use of loop primers in a pyrophosphate SNP detection method (see page 16, paragraph 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Ahmadian in view of Barany with the use of loop primers as taught by Dzieglewska since Dzieglewska states that the use of the loop primer avoids the possibility of the hybridized primer being washed away during the protocol (see page 16, paragraph 2). So an ordinary practitioner, concerned about removing primers during the manipulations of the method of Ahmadian in view of Barany would have been motivated to use the loop primers of Dzieglewska since Dzieglewska expressly teaches their use in a pyrophosphatase sequence determination method, the identical basic technology of the current claims.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1634